REMARKS

Claims 401, 411, 412, 414, 416-419, 422-424, 437-438 and 462-468 are pending. Claims 402-410, 413, 421, 425-436 and 439-461 are cancelled without prejudice. Applicants reserve the right to pursue the subject matter of these claims in one or more continuing applications. Claims 401, 411, 412, 419, 422, 423, 437, 438, 462 and 463 are amended. Claims 464-468 are added. Support for such amendments is found throughout the instant specification, for example, page 137, lines 16-26 and Figure 14, and page 72, lines 3-7. No new matter is added.

In support of the remarks and arguments stated *infra*, Applicants have submitted herewith the Declaration of Dr. Tony Peled under 37 C.F.R. §1.132 ("Peled Declaration").

35 U.S.C. § 112, First Paragraph, Rejections

The Examiner has rejected claims 401, 411-412, 414-425, 434, 436-438 and 462 under 35 U.S.C. 112, first paragraph as lacking proper enablement in the instant specification. The Examiner, while acknowledging that the specification is enabling for a method of expanding an *ex-vivo* population of CD34+ and CD34+CD38- hematopoietic stem cells in culture, while at the same time inhibiting differentiation of said cells, the method comprising:

> (a) providing hematopoietic CD34+ cells that are not enriched prior to culturing, culturing said CD34+ cell cultures *ex-vivo* under conditions allowing for cell proliferation, wherein said conditions comprise a combination of cytokines selected from the group consisting of stem cell factor, TPO, FLt3, IL-6 and IL-3, and
> (b) culturing said CD34+ cell cultures in the presence of concentrations of 1-10 mM of exogenously added nicotinamide for up to three weeks culturing period;
> thereby expanding said population of said hematopoietic stem cells while inhibiting the differentiation of said CD34+ cell cultures *ex-vivo* in culture medium,

the Examiner asserts that the specification fails to provide enablement for expanding any other population of stem cells or for culturing the cell cultures in any other conditions for proliferation (emphasis added). *See*, Office Action at pages 4-6.

Applicants disagree. However, in the interested of expediting prosecution, claims 401, 411, 412 and 462, from which the remaining claims subject to the rejection depend, are amended herein to recite "CD34+ hematopoietic cells", "a combination of cytokines selected from the group consisting of stem cell factor, thrombopoietin, FLt3 ligand, IL-6 and IL-3" and "presence of about 1.0 mM to about 10 mM exogenously added nicotinamide, nicotinamide

analog or nicotinamide derivative", which as stated by the Examiner are enabled by the instant specification. Applicants traverse the remaining rejections with respect to the pending claims as amended and added herein.

The Examiner has also asserted that the limitations "hematopoietic CD34+ cells that are not enriched prior to culturing" and "culturing said CD34+ cell cultures in the presence of ...exogenously added nicotinamide for up to three weeks culture period" are essential to the claimed invention. Applicants disagree.

The instant specification does not require the use of an unselected source of hematopoietic stem cells for expansion with nicotinamide or other inhibitors of CD38, nor is such a feature essential to the claimed invention, as suggested by the Examiner. For example, Example 1 discloses the expansion of the CD34+ cell compartment from both selected and unselected (mononuclear cells) sources of CD34+ cells. Further, Example 5 at page 137 readily shows the ability of nicotinamide to inhibit differentiation and enhance expansion of hematopoietic stem cells from pre-selected CD34+ donor cells. Thus, Applicant submits that one or ordinary skill in the art reading the application at the time of filing (including original claims 417 and 418) would readily recognize that expanding "hematopoietic CD34+ cells that are not enriched prior to culturing" is not an essential feature as suggested by the Examiner, but rather only one embodiment for practicing the claimed invention.

The instant specification also does not require the culturing of the cells "for up to three weeks", nor is such a feature essential to the claimed invention, as suggested by the Examiner. In contrast, the instant specification provides numerous examples of the superior expansion of hematopoietic stem cells using inhibitors of CD38 over periods ranging from 2 weeks to 11 weeks or more, for up to three weeks at the onset of culturing, or continuously during the culture period. Further, using the methods disclosed in the instant specification, the inventors have shown that continued culture of hematopoietic cells in the presence of nicotinamide for five weeks results in consistent expansion of CD34+ cells, and exponential expansion of the early progenitor CD34+/CD38- and CD34+/Lin- cell subsets. *See*, Peled Declaration at pages 2-5. Thus, Applicant submits that one or ordinary skill in the art reading the application at the time of filing would readily recognize that culturing cells "up to three weeks" is not an essential feature as suggested by the Examiner, but rather only one embodiment for practicing the claimed invention.

In view of the foregoing arguments and amendments, Applicants submit that one of ordinary skill in the art would be able to use the claimed methods, as taught, without undue experimentation. Reconsideration and withdrawal of the instant rejections is therefore respectfully requested.

35 U.S.C. § 103(a) Rejections

The Examiner has rejected claims 401, 411, 412, 414, 416-418, 421-425, 434, 436-438, 460 and 462 under 35 U.S.C. § 103(a) as being anticipated by US Patent Publication No. 2002/0159984) to Brown ("Brown"). *See*, Office Action at pages 7-6.

Applicants traverse the rejection with respect to the pending claims as amended and added herein.

The Examiner asserts that Brown teaches *ex-vivo* expansion of hematopoietic stem cells derived from cord blood in the absence of serum, in a culture medium comprising nutrients and growth factors and cytokines, resulting in significant expansion of CD34+CD38- cells at day 3, 7 and 14, which can be used for long term engraftment, wherein the medium (IMDM) can be reformulated to contain essential components in amounts 0.1 to 10...times their amounts. Specifically, as suggested by the Examiner, at best Brown teaches the medium may have up to 10 times the 4mg/liter (0.033 mM) of nicotinamide, specifically described.

Applicants submit that Brown does not teach or suggest "...about 1.0 to about 10 mM nicotinamide..." as required by independent claims 401, 411, 412 and 462 as amended herein. Applicants further submit that this critical feature is not taught or suggested by Brown. Brown merely teaches that nicotinamide is one of a number of "...various vitamins and co-factors, such as riboflavin, nicotinamide, folic acid, choline, biotin, and the like that may be required to sustain cell growth." *See*, Brown at ¶ [0040]. Brown does not teach or suggest that nicotinamide is an essential component of the medium, and further Brown does teach or suggest that the addition of nicotinamide in concentrations greater than the 4mg/liter cited in Table 1, is used for the inhibition of differentiation of hematopoietic stem cells.

As such, Applicants respectfully request reconsideration and withdrawal of the present rejection.

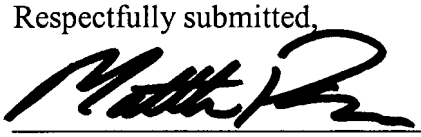
Double Patenting Rejections

Claim 411 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as unpatentable over claim 208 of co-pending U.S. Application No. 10/767,064. Claim 208 of co-pending U.S. Application No. 10/767,064 is cancelled. Therefore, this rejection is moot and should be withdrawn.

CONCLUSION

On the basis of the foregoing amendments, Applicants respectfully submit that the pending claims are in condition for allowance. Should any questions or issues arise concerning this application, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,



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